

[FOREWORD](#)

[INTRODUCTION](#)

**HEXAMETHYLENE GLYCOL**  
**CAS N°: 629-11-8**

**SIDS INITIAL ASSESSMENT PROFILE**

<b>CAS Nr.</b>	629-11-8
<b>Chemical Name</b>	Hexamethylene glycol
<b>Structural formula</b>	HO-(CH <sub>2</sub> ) <sub>6</sub> -OH
<b><u>CONCLUSIONS AND RECOMMENDATIONS</u></b>	
It is currently considered of low potential risk and low priority for further work.	
<b><u>SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS</u></b>	
<p>The production volume of this chemical in Germany was 10,000-50,000t in 1991. The total production volume is used as an intermediate in chemical industry for the synthesis of polyesters and polyesterol-type polyurethanes, which are used for paints, laquers and varnishes.</p> <p>The substance has no considerable potential for bio- and geoaccumulation. (log P<sub>ow</sub> 0.0) It is readily biodegradable. In water, hydrolysis or photolysis are unlikely to occur.</p> <p>The following aquatic effects concentrations are available: <i>Leuciscus idus</i>: 460-1000mg/l(LC<sub>50</sub>, 96h:), <i>Daphnia magna</i> &gt;500mg/l(EC<sub>50</sub>, 24h&amp;48h:), <i>scenedesmus subspicatus</i>: 2200 mg/l (EC50, 72h). From these data a PNECaqua of 500µg/l was derived. No data are available on terrestrial organisms.</p> <p>For production and processing PECs of 0.19µg/l (site specific) and 29µg/l (generic) were estimated. With a PNECaqua of 500µg/l, the PEC/PNEC ratio is calculated as less than 1. Therefore no risk to the aquatic environment is to be expected. A significant exposure to the terrestrial compartment could not be identified.</p> <p>This chemical is not acutely toxic. It is considered as non-irritating to the skin and only slightly irritating to the eyes. No skin sensitising potential was revealed. 28 day repeated dose testing in rats revealed slight effect upon body weight in males or females at 1000mg/kg bw/day. The oral NOAEL was determined as 400 mg/kg bw/day. No indication of toxic effects on reproductive function or developmental toxicity were observed. Neither mutagenic nor clastogenic potential could be detected in <i>in vitro</i> tests with this chemical. No <i>in vivo</i> mutagenicity testing has been performed.</p> <p>This chemical has very low toxic potential, and no local or organ-specific effects were detected. The toxic potency is also low Under "worst-condition-assumptions" for workers, a risk can not be identified. There is no reason to assume consumer exposure.</p>	
<b><u>IF FURTHER WORK IS RECOMMENDED, SUMMARISE ITS NATURE</u></b>	
No further work is recommended.	

## SIDS PROFILE SUMMARY

CAS-NO.: 629-11-8			PROTOCOL	RESULTS
<b>PHYSICAL CHEMICAL</b>				
2.1	Melting Point		NA	40-42 °C
2.2	Boiling Point		NA	243 °C (at101.3 kPa)
2.3	Density		DIN 51 757	960 kg/m <sup>3</sup>
2.4	Vapour Pressure		NA	< 0.01 hPa at20°C
2.5	Partition Coefficient (Log Pow)		OECD 107	0
2.6 A	Water solubility			miscible at 20°C
2.12	Oxidation : Reduction potential			mV
<b>ENVIRONMENTAL FATE / BIODEGRADATION</b>				
3.1.1	Photodegradation		calc. (Atkinson)	In air T <sub>1/2</sub> = 28.8 hour
3.3	Transport and Distribution		calculated (fugacity level 1 type)	In air % In water 99 % In sediment % In soil % In biota %
3.5	Biodegradation		OECD 301 C	readily biodegradable
<b>ECOTOXICOLOGY</b>				
4.1	acute/prolonged toxicity to fish	Leuciscus idus	DIN 38 412 / 15	LC <sub>50</sub> (96hr) = 460-1000 mg/l
4.2	acute/prolonged toxicity to aquatic invertebrates ( daphnia )	Daphnia magna	84 / 449 / EEC, C.2	EC <sub>50</sub> (48hr) = > 500mg/l
4.3	toxicity to aquatic plants e. g. algae	Scenedesmus subspicatus	DIN 38 412 / 9	EC <sub>50</sub> (72hr) = 2200mg/l EC <sub>10</sub> (72hr) = 810mg/l
<b>TOXICOLOGY</b>				
5.1.1	acute oral toxicity	rat	NA	LD <sub>50</sub> = 3000 mg/kg
5.1.2	acute inhalation toxicity			LC <sub>50</sub> = mg/m <sup>3</sup>
5.1.3	acute dermal toxicity	rabbit	NA	LD <sub>50</sub> > 10000mg/kg
5.4	repeated dose toxicity	rat	OECD 407	NOAEL = 400mg/kg
5.5	genetic toxicity in vitro			

A.	bacterial test (gen mutation)	Ames	OECD 471	- (with metabolic activation) - (without metabolic activation)
	non-bacterial test (gene mutation)	CHO- HPRT	OECD 476	- (with metabolic activation) - (without metabolic activation)
B.	mammalian cytogenetic in vitro test (chromosomal aberration)	CHO- V79	OECD 473	- (with metabolic activation) - (without metabolic activation)
5.6	genetic toxicity in vivo			
5.8	toxicity to reproduction	rat	OECD 421	NOAEL = 400 mg/Kg (rep. tox. parental, male) NOAEL = 1000mg/Kg (rep. tox. parental, female)
5.9	developmental toxicity / teratogenicity	rat	OECD 421	NOEL = 1000mg/Kg (pregnancy/litter) NOEL = 1000mg/Kg (foetal data)
5.11	experience with human exposure			

# SIDS Initial Assessment Report

## 1. Identity

Name:	Hexane-1,6-diol
CAS-No.:	629-11-8
Empirical formula:	C <sub>6</sub> H <sub>14</sub> O <sub>2</sub>
Structural formula:	HO-(CH <sub>2</sub> ) <sub>6</sub> -OH
Synonyms:	Hexanediol Hexanediol 1,6-Dihydroxyhexane 1,6-Hexanediol Hexamethylene glycol Hexamethylenediol Hexan-1,6-diol
Degree of purity:	> 96%

## 2. General Information on Exposure

The production level of Hexane-1,6-diol in Germany was 10,000-50,000 t in 1991. There is no information about export and import volumes.

The production capacity in Japan and USA was 8,500 t resp. 6,000 t in 1987. There are no data available from other countries.

All the produced Hexane-1,6-diol is used as an intermediate in chemical industry for the synthesis of polyesters and polyesterol-type polyurethanes, which are used for paints, laquers and varnishes.

During production and processing in Germany, about 0.8 kg/t production volume were emitted into the waste water by one German producer. Exhaust gases are burnt in an incinerator.

Supposing a residual concentration of monomeres in the polyesters, an unknown amount of Hexane-1,6-diol is entering the environment during the life of the polymeres.

## 3. Environment

### **3.1 Environmental Exposure**

#### **3.1.1 General Discussion**

Hexane-1,6-diol is miscible with water at 20 °C and has a vapour pressure of <0.01 hPa at 20°C. Its measured log Pow of 0.0 indicates that there is no considerable potential for bio- and geoaccumulation.

Based on the physico-chemical properties, the preferred environmental compartment of Hexane-1,6-diol is the hydrosphere (Mackay I: 99%).

Hexane-1,6-diol is biologically readily degradable. According to the model SIMPLETREAT (cf. Ref.1), in wwpt's a removal rate of 91% is predicted.

In water solution, hydrolysis or photolysis are not likely to occur.

The calculated half-life due to photochemical-oxidative degradation in the atmosphere by OH-radicals is about 1.2 days.

### 3.1.2 Predicted Environmental Concentration

#### a. Point emissions

For production and processing of Hexane-1,6-diol, we would consider the following scenario: Based on a maximum production volume of 50,000 t/a and an emission rate of 0.8 kg/t during production and processing a total amount of 40 t/a is emitted into the waste water by one German producer. With an elimination factor of 91 % in the sewage treatment plant, 3.6 t/a are emitted into the river Rhine. The flow-rate (10%ile) is 734 m<sup>3</sup>/s and therefore the predicted environmental concentration is calculated to:

$$\text{PEC} = \frac{3.6 \text{ t/a}}{734 \text{ m}^3/\text{s}} = 0.19 \text{ } \mu\text{g/l}$$

In addition the PEC<sub>local</sub> is calculated using a generic exposure model. Based on a maximum production volume of 50,000 t/a and an emission rate of 0.3 % during production and 0.7 % during processing (Emission Scenario Documents in (1)), a total amount of 500 t/a is emitted into the waste water. With an elimination factor of 91% in the treatment plant, 45 t/a are emitted into the environment. A flow-rate of the receiving river of 60 m<sup>3</sup>/s is assumed as default value (Emission Scenario Document in (1)).

The predicted environmental concentration is

$$\text{PEC} = \frac{45 \text{ t/a}}{60 \text{ m}^3/\text{s}} = 29 \text{ } \mu\text{g/l}$$

#### b. Diffuse emissions

An unknown amount of Hexane-1,6-diol residual monomere from polyesters is entering into atmosphere and hydrosphere. Because of the fast degradability in both compartments and the diffuse release, significant concentrations in the environment are not to be expected.

## 3.2 Effects on the Environment

### 3.2.1 Aquatic effects

#### Available data

The following ecotoxicological effect concentrations, corresponding to the aquatic environment, are available:

a) fish

*Leuciscus idus* LC<sub>50</sub> = 460-1000 mg/l (96h)  
(test substance: Hexane-1,6-diol crude 65%)

*Leuciscus idus* LC<sub>50</sub> = 4600-10000 mg/l (96h)  
(test substance: Hexane-1,6-diol flakes)

Note: The different results are probably caused by impurities in the technical product.

b) invertebrates

*Daphnia magna* EC<sub>50</sub> > 500 mg/l (24 and 48h)  
(effect: immobilisation)

c) algae

*Scenedesmus subspicatus* EC<sub>50</sub> = 2200 mg/l (72h)  
EC<sub>10</sub> = 810 mg/l (72h)  
(effect: growth inhibition, biomass)

d) bacteria

*Pseudomonas putida* EC<sub>50</sub> > 10000 mg/l (17h)  
EC<sub>10</sub> = 8400 mg/l (17h)  
(effect: cell multiplication inhibition)

*Pseudomonas putida* EC<sub>10</sub> = 5200 mg/l (18 h)  
(effect: cell multiplication inhibition)

activated sludge (industrial) EC<sub>0</sub> = 1000 mg/l (30 min)  
EC<sub>10</sub> > 1000 mg/l (30 min)  
(effect: inhibition of oxygen consumption)

*Photobacterium phosphoreum* EC<sub>50</sub> = 205 mg/l (30 min)  
(effect: inhibition of light emission)

### Determination of PNEC<sub>aqua</sub>

There are data from short-term tests with three trophic levels available. An assessment factor of 1000 is applied to the lowest effect value of 500 mg/l derived from tests with *Leuciscus idus* and *Daphnia magna*.

Therefore: PNEC<sub>aqua</sub> = 500 mg/l / 1000 = 500 µg/l

### 3.2.2 Terrestrial organisms

There are no data available on terrestrial organisms.

### 3.3 Initial Assessment for the Environment

With the PECs of 0.19 µg/l and 29 µg/l (site-specific resp. generic model) and a PNEC<sub>aqua</sub> of 500 µg/l PEC/PNEC ratios of  $3.8 \cdot 10^{-4}$  and  $5.8 \cdot 10^{-2}$  can be calculated. Therefore, at present no risk to the aquatic environment is to be expected.

A significant exposure to the terrestrial compartment could not be identified. Further work is presently not necessary for a risk assessment for this compartment.

## 4. Human Health

### 4.1. Human Exposure

Hexanediol is an intermediate in chemical industry for the synthesis of polyesters and polyesterol-type polyurethanes, which are used for paints, laquers and varnishes. Production and further processing is performed in closed systems. It is assumed that hexanediol is completely converted to the end products. Measurements of residual hexanediol concentrations in reaction products are not available. On the other hand hexanediol is readily biodegradable and has no considerable potential for bio- or geoaccumulation. Thus it can be concluded that exposure for consumers and also for humans via the environment is negligible as laid out in previous chapters. Workers can be exposed during filling or routine analysis at production sites.

#### 4.1.1 Workers

Workers can be exposed during filling or routine analytical sampling. The maximum product temperature is 80°C. No work place analysis has been performed.

A "worst case assessment" has been made using the model "EASE". Assuming a product temperature of 80°C a concentration range of 100 -200 ppm hexanediol has been calculated using LEV (local exhaust ventilation). During routine production without product emission concentrations between 0 and 0.1 ppm have been calculated. The high value of 200 ppm is representing a theoretical exposure during the sampling procedure without protective measures other than local exhaust ventilation. Due to the required use of personal protection measures this high exposure can be ruled out. For workplace assessment the predicted upper value of 0,1 ppm during routine production can be used as 'worst case'.

#### 4.1.2 Consumers

Hexanediol is an intermediate in chemical industry for the synthesis of polyesters and polyesterol-type polyurethanes, which are used for paints, laquers and varnishes. It is assumed that hexanediol is completely converted to the end products. On the other hand hexanediol is readily biodegradable and has no considerable potential for bio- or geoaccumulation. Thus it can be concluded that exposure for consumers is negligible low as laid out in previous chapters.

#### 4.1.3 Population exposed via the environment

Based on the information given in chapter 4.3.1 it can also be concluded that exposure for humans via the environment is negligible.

## 4.2 Effects on Humans

Although the technical synthesis of hexanediol has already been published 1932 [21], no adverse effects on humans have been reported in the literature. Therefore, also information from animal and in vitro studies is presented.

### a) mode of action of the chemical, toxicokinetics and metabolism

There are no detailed studies with respect to toxicokinetics or metabolism. However, based on the structure and shown after oral application to rabbits (26), oxidation of both alcohol-groups resulting in the formation of adipic acid was observed. The toxic profile of this dicarbonic acid has been well examined [2, 27].

No signs of cytotoxicity or intermediary filaments in a human skin fibroblast culture were noted after hexanediol exposure of 16 mM over 14 days and 8 mM over 60 days. [23]

A series of homologous n-alkanols and n-alkanediols was tested for inhibition of K<sup>+</sup> ion flux through a Ca<sup>2+</sup>-activated channel in rat glioma cells. The 50 % inhibitory concentration (IC<sub>50</sub>) is 3.5 times more potent for hexanediol than for n-hexanol. This was interpreted as a direct effect on protein involved in the inhibitory action rather than only lipid solubility criteria [22].

### b) acute toxicity

#### - acute oral/inhalation/dermal toxicity

The acute oral toxicity was tested in rats with comparable LD<sub>50</sub> values of 3,000 mg/kg b.w. [3] or 3,730 mg/kg b.w. [4,5] Hexanediol was not lethal to 3 rabbits given 3,000 mg/kg b.w. by gavage [6]. Two cats dosed once with 300 mg/kg b.w. by gavage survived, while 2 out of 4 animals receiving 1,000 mg/kg b.w. died. No mortality was observed when six rats were exposed to an atmosphere that had been saturated at 100 degrees centigrade with the vapor of the substance [3]. This holds also for eight rats exposed at room temperature for 8 hours to the volatile part of the compound [4]. No mortality occurred when 5 rabbits/sex received 2,500 mg/kg b.w. for eight hours dermally under occlusive conditions [7]. Another author reported an LD<sub>50</sub> > 10,000 mg/kg after dermal application of rabbits [4,5]. Comparable LD<sub>50</sub> values (about 2,300 and 1,738 mg/kg b.w.) were noted for mice after intraperitoneal application [3 and 8,9].

#### Conclusion:

The available data are sufficient for Initial Hazard Assessment. The data indicate that Hexanediol is not acute toxic and has not to be classified according to EU-criteria.

#### - irritation

An 80% aqueous preparation of hexanediol was not irritating to rabbit skin after up to 20h occlusive exposure [3]. In another study the irritation index according to Smyth-Carpenter reached 2 out of 10 points, which is considered to be not irritant [4]. Eye irritation was tested in rabbits according to the method of Draize. Initial findings were slight chemosis and slight corneal opacity. The findings were completely reversible within 8 days after application [3]. In another eye irritation study

according to the method of Smyth-Carpenter the compound reached grade 3 on a 10 point scale indicating an irritant effect based on this grading scheme [4].

**Conclusion:**

The available data are sufficient for Initial Hazard Assessment. Hexanediol is considered as not irritant to the skin and only slightly irritant to the eyes. According to EU-criteria it has not to be classified as irritant.

**- sensitization**

In a Guinea pig maximization test according to the method of Magnusson and Kligman (OECD 406) Hexanediol was not sensitizing [10]. The intradermal induction was performed with 5%, while the dermal induction (48 hours occlusive exposure) was performed with a concentration of 50%. The challenge concentration was 25% (24 hours occlusive exposure). Water was used as vehicle in this study. There was no indication that Hexanediol is a skin sensitizer.

**Conclusion:**

No skin sensitizing potential.

**c) repeated dose toxicity**

Male and female Wistar rats received 0, 100, 400 and 1,000 mg/kg b.w. Hexanediol by gavage for 28 days in compliance with OECD test method 407 to assess the effect of hexanediol with respect to repeated toxicity and for 28 days (males) / 42 days (females) in compliance with OECD test method 421. There were no clinical, clinico-chemical, hematological parameters adversely affected in these studies. In addition no test substance-related gross- or histopathological alterations were noted in these studies. Slight changes in body weight and body weight gain at 1000 mg/kg b.w./d were observed always only in one sex: females (OECD 407) and males (OECD 421). This effect is assessed as a borderline effect of questionable toxicological relevance because of the following reasons: only one sex (either males or females) is affected; there is no correlation to foods consumption, no changes in hematology, clinical chemistry and histopathology were found. The NOAEL is 400 mg/kg b.w. for male and female rats [13, 20]. Other repeated dose toxicity studies were performed with non relevant routes of administration (intraperitoneal [14,15], subcutaneous [16]) or animal species not routinely considered as relevant for the assessment of repeated dose toxicity [6]. Compared to the above mentioned OECD 407 study, the studies lack an appropriate study design due to limited scope of examination such as low number of animals, limited scope of examination including histopathology [6, 14, 15, 16].

**Conclusion:**

In valid OECD studies, tested up to the highest recommended dose of 1,000 mg/kg b.w. hexanediol revealed no effects of toxicological relevance beside a borderline effect on body weight either in males (OECD 421) or in females (OECD 407). NOAEL = 400 mg/kg b.w..

**d) reproduction/developmental toxicity**

Male and female Wistar rats received 0, 100, 400 and 1,000 mg/kg body weight Hexanediol by gavage for 4 (males) to 6 (females) weeks in compliance with OECD test method 421 to screen the effect of hexanediol on reproduction and developmental toxicity. The pre-mating exposure period was at least 14 days and the study was terminated 4 days post partum of the F1 generation pups. Marginal retarded body weight development in males at 1,000 mg/kg b.w. was the only effects noted in this study. This dose level represent the highest concentration required for this type of

study. There were no signs indicating impairment of reproductive function of F0 rats and no signs of developmental toxicity in their offspring. The NOAEL for parental toxicity is 400 mg/kg b.w. (males) and 1,000 mg/kg b.w. (females). The NOAEL for reproductive function and development toxicity is 1,000 mg/kg b.w.[20].

**Conclusion:**

In a valid OECD 421 study no indication of toxic effect on reproductive function or developmental toxicity were observed.

**e) genetic toxicity**

Hexandiol was not mutagenic in the Ames test (OECD 471) when *Salmonella typhimurium* strains (TA 98, TA 100, TA 1535 and TA 1537) were exposed up to 5,000 µg/plate with and without metabolic activation [17]. In vitro point mutation was also studied in mammalian cells (Chinese hamster V79 HPRT locus, OECD 476) with no indication of a mutagenic response either in the presence or absence of metabolic activation [19]. This holds also for chromosome aberration according to OECD 473 performed with the same cell line with and without S9 mix [18]. In the absence of positive mutagenicity data in vitro no in vivo mutagenicity studies have been performed.

These data indicate that Hexanediol has no mutagenic potential in the above described in vitro assays. No in vivo mutagenicity studies have been performed.

**Conclusion:**

Neither a mutagenic nor a clastogenic potential could be detected in in vitro tests with Hexanediol. No in vivo mutagenicity studies have been performed.

**f) any other human health related information that is available**

1,6-Hexanediol and 2,5 Hexanediol have been tested for neurotoxic effects. Rats were receiving 0,5% Hexanediol (500 mg/kg b.w.) via the drinking water over a period of 12 weeks. In contrast to 2,5-hexanedione no signs of neurotoxicity or histopathological alteration of nervous tissue was observed with 1,6-hexanediol [11, 12].

Hexanediol did not inhibit the glyceraldehyde-3-phosphatase dehydrogenase activity of the nervous system in vitro as did, for example the neurotoxic hexacarbon compound 2,5-hexanedione [25].

After local application to the nervous tissue hexanediol caused no and 2,5-hexanedione caused changes of the neurofilaments and swelling of Schwann's cells [24]. This correlated with the above described in vivo neurotoxicity studies.

Other information relevant for the risk assessment with human health is not available.

### **4.3 Initial Assessment for Human Health**

As shown in chapter 4.2 hexanediol has a very low toxic potential: no local or organ-specific effects were detected. The toxic potency is also low: the lowest NOAEL has been derived in the OECD Test 421 the effect observed (reduced body weight development in adult male rats) is representing a systemic effect not related to reproductive/developmental toxicity. Compared to the 28 day gavage study in the same rat species (OECD 407), the effect was somewhat more pronounced and statistical significant ( $P < 0.05$ ) in the OECD 421 test. At study termination bodyweight only of male rats was

5% lower when compared to the untreated control indicating a toxicological effect of borderline significance. 400 mg/kg is taken as a NOAEL for repeated application.

#### 4.3.1 Workers

Assuming 100% resorption, an inhaled air volume of 10 m<sup>3</sup>/8 h working day and estimated (worst-case) concentration of 0.1 ppm, the EHE for a 70 kg worker will be 5 mg hexanediol/working day corresponding to 0,07 mg/kg/d.

Comparing this estimated dose with the NOAEL, a very high margin of safety of

$$\frac{\text{NOAEL } 400 \text{ mg/kg/d}}{\text{EHE } 0,07 \text{ mg/kg/d}} = \frac{\text{-----}}{\text{-----}} = 5,714$$

is estimated. Even under "worst-condition-assumptions" a risk cannot be identified. Hexanediol is considered as of low potential for risk to man.

#### 4.3.2 Consumers

Following the assessment of the use of the substance and the exposure scenario, there is no reason to assume relevant consumer exposure. Taking into account the inherent toxicity of the substance, there is no reason for concern; the substance is considered of low potential risk and low priority for further work.

#### 4.3.3 Population exposed via the environment

According to the ready biodegradability in the environment a very low potential for risk to man is assessed.

## **5. Conclusions and Recommendations**

### **5.1 Conclusions**

#### **Environment:**

The risk assessment for the aquatic compartment showed that PEC/PNEC < 1. On the whole, Hexane-1,6-diol is of low concern to the environment.

#### **Human health:**

Taking into account the inherent toxicity of the substance, there is no reason for concern; the substance is considered of low potential risk and low priority for further work.

### **5.2 Recommendations**

No further tests are needed.

## **6. References**

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